Annals of Surgical Oncology **15**(4):1001–1007
DOI: 10.1245/s10434-007-9559-5

Liver Transplantation for Hepatocellular Carcinoma

Vincenzo Mazzaferro, MD,[1] Yun Shin Chun, MD,[2] Ronnie T. P. Poon, MS, PhD,[3] Myron E. Schwartz, MD,[4] Francis Y. Yao, MD,[5] J. Wallis Marsh, MD,[6] Sherrie Bhoori, MD,[1] and Sung-Gyu Lee, MD, PhD[7]

[1]Department of Surgery, National Cancer Institute, Milan, Italy
[2]Department of Surgical Oncology, University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA
[3]Department of Surgery, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China
[4]The Recanati/Miller Transplantation Institute and Department of Surgery, The Mount Sinai Hospital, New York, New York, USA
[5]Department of Medicine, Division of Gastroenterology, University of California, San Francisco, San Francisco, California
[6]Department of Surgery, Thomas E. Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, Pennsylvania
[7]Department of Surgery, Hepato-Biliary Surgery and Liver Transplantation, Asan Medical Center, Ulsan University, Seoul, Korea

Background: Orthotopic liver transplantation (OLT) is the best available option for early hepatocellular carcinoma (HCC), although its application is limited by stringent selection criteria, costs, and deceased donor graft shortage, particularly in Asia, where living donor liver transplant (LDLT) has been developed.

Methods: This article reviews the present standards for patient selection represented by size-and-number criteria with particular references to Milan Criteria and novel prediction models based on results achieved in patients exceeding those limits, with consideration of the expanded indication represented by the UCSF Criteria.

Results: The expected outcomes after deceased donor liver transplant (DDLT) or LDLT are favorable if predetermined selection criteria are applied. However, selection bias, difference in waiting time, and ischemia-regeneration injuries of the graft among DDLT vs LDLT may influence long-term results. In the article, the differences between East and West in first-line treatments for HCC (resection vs transplantation), indications, and ethics for the donor, are summarized as well as possible novel predictors of tumor biology (especially DNA mutation and fractional allelic loss, FAI) to be considered for better outcome prediction.

Conclusions: Liver transplantation remains the most promising product of modern surgery and represents a cornerstone in the management of patients with HCC.

Key Words: Hepatocellular—Hepatoma—Transplantation.

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide.[1] Orthotopic liver transplantation (OLT) is the best therapeutic option for early, unresectable HCC, although it is limited by graft shortage and the need for appropriate patient selection. In the late 1980s, the results after OLT for HCC were disappointing, with high early recurrence and 5-year survival rates ranging between 18 and 40%.[2] This discouraging experience and shortage of deceased donor grafts compelled the transplant community to establish stringent selection criteria to predict posttransplant survival of HCC patients. Recognizing that patients with small, incidentally found tumors had survival rates after liver transplantation equivalent to those after transplantation for benign disease, Mazzaferro et al. in Milan established criteria for OLT in a landmark

Received June 1, 2007; accepted July 7, 2007; published online January 31, 2008.
Proceedings of the Fifth International Meeting Hepatocellular Carcinoma: Eastern and Western Experiences held in Houston, TX, January 11–13, 2007.
Address correspondence and reprint requests to: Sung-Gyu Lee, MD, PhD; E-mail: sglee2@amc.seoul.kr

study published in 1996.[3] They showed that a subgroup of patients with radiologic evidence of a single tumor ≤5 cm in diameter, or two to three tumors ≤3 cm in diameter had 5-year and recurrence-free survival rates of 75 and 83%, respectively. The Milan criteria were subsequently adopted by the United Network for Organ Sharing (UNOS) staging system for allocating organs for OLT in the United States.

OLT is limited by a shortage of deceased donor liver grafts, particularly in Asia, where the rate of deceased donors is negligible. To overcome this shortage, living donor liver transplantation (LDLT) has been developed with favorable preliminary results. Other areas of study include expanding the criteria for liver transplantation to include larger tumors, as shown by the group from the University of California, San Francisco (UCSF) and molecular profiling of HCC to improve prognostication and patient selection.

MILAN CRITERIA FOR LIVER TRANSPLANTATION IN HCC

In the past 10 years, results of OLT have improved steadily because of careful patient selection pioneered by the introduction of the Conventional Milan Criteria (CMC) in 1996.[3] The aim of these criteria was to achieve a good outcome in patients who fulfilled the criteria and avoid a poor prognosis in patients who exceeded them. This aim was achieved by the Milan group, who showed that the 10-year overall survival surpassed 70% in 300 liver transplants for HCC that fulfilled the CMC. Such good results have been confirmed worldwide.[4,5] The elements of the CMC, namely size and number of tumors, have been shown in multivariate analysis to be the only independent variables predicting patient survival and tumor recurrence, with other biological prognostic factors playing a role only within the ''size and number'' limits (Table 1).

The successful outcome of OLT based on the CMC has led to more patients with HCC being routed to transplantation and an increasing number of proposals for expansion of the CMC.[6,7] None of these expanded criteria are, however, supported by a robust statistical sample size or prospective validation. In order to investigate proposals to expand the CMC, an unprecedented multicenter study has been conducted in 24 European centers, collecting data from 466 patients transplanted for HCC whose tumors exceeded the CMC at posttransplant pathologic assessment (http://www.hcc-olt-metroticket.org).[5,7]

TABLE 1. *Prognostic factors affecting survival of 250 patients transplanted for HCC according to Conventional Milan Criteria at the National Cancer Institute of Milan*

10-year survival: multivariate analysis

Variable	HR	CI (95%)	*P* value
Overall patient survival			
Conventional Milan criteria (in vs out)	3.1	1.35–6.93	.007
Tumor-free survival			
Conventional Milan criteria (in vs out)	5.5	1.39–21.27	.01
Microsatellites (yes vs no)	3.6	1.5–8.71	.004
Microvascular invasion (yes vs no)	3.4	1.36–8.76	.009
Tumor grading (G3 vs G1-2)	3.4	1.04–11.14	.04

The results have been plotted in a tumor size-and-number Cartesian contour plot showing the 5-year survival probability according to the size and number of HCC nodules detected in the explanted liver. Based on a preliminary analysis, a ''HCC forecast chart'' has been developed, which can predict 5-year posttransplant survival rates on the basis of morphological tumor characteristics (Fig. 1). It is conceivable that similar chart models obtained from large sample sizes could replace the CMC for OLT in patients with HCC. Unlike the CMC or expanded proposals, which are based on tumor morphology, these chart models can incorporate important variables for OLT in HCC, including priority score for HCC and dropout rate based on donor availability at different centers. Preliminary ad interim analysis shows a significant shift of the isograms of the proposed chart depending on the presence of vascular invasion in explant specimens, confirming the need for reliable biological markers of important tumor characteristics, such as vascular invasion.

MILAN VERSUS EXPANDED CRITERIA FOR LIVER TRANSPLANTATION

Following the 1996 publication by the group from Milan, using a restrictive set of criteria for OLT in patients with HCC, excellent 5-year posttransplant patient survival of at least 70% has been reported from many centers.[4,5] The growing experience and success of OLT for HCC have fueled controversies related to expansion of the Milan criteria for OLT, since many studies have suggested that tumor stage beyond the Milan criteria does not necessarily predict worse survival after OLT.[8,9] Among the proposed expanded criteria, the UCSF criteria (single tumor nodule up to 6.5 cm; or three or fewer tumors, the largest of which is ≤4.5 cm with the sum of the tumor diameters ≤8 cm) reflect a modest expansion of tumor

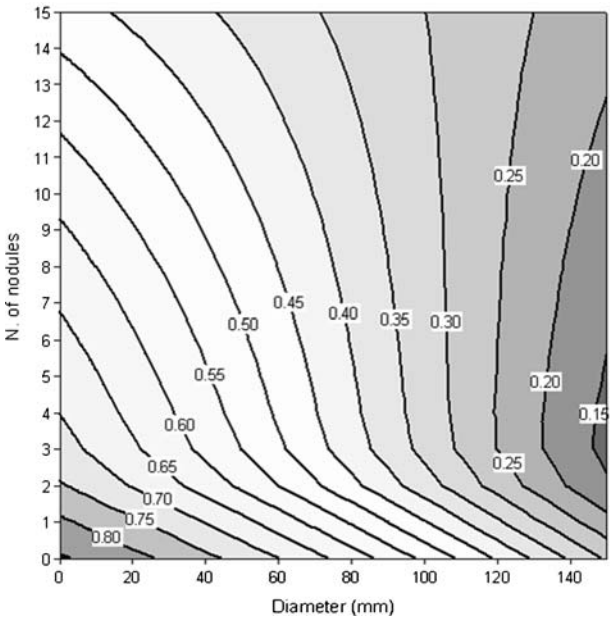

FIG. 1. HCC forecast chart showing probability of 5-year survival based on tumor size and number in explanted liver.

size limits beyond the Milan criteria.[6] At least three transplant experiences from Europe and the United States, however, underlined the limitations of applicability of the UCSF criteria in the pretransplant setting, considering that most of the patients adhering to the UCSF were also within the Milan criteria.[10–12] Even though the UCSF criteria have been independently validated in several studies, the overlapping population of patients adhering to the UCSF but not the Milan criteria is often negligible and estimated to be $<10\%$ of the total transplanted population.[12,13] Such a limitation was evidenced by a multicenter study from France, in which 39 of 461 patients (8.7%) had explanted tumors beyond the Milan but within the UCSF criteria.[10] Although the 5-year survival of 67% for patients within the UCSF criteria was equivalent to that of the 183 patients meeting the Milan criteria (and significantly better than the 34% 5-year survival rate among 238 patients exceeding both criteria), the 44 patients meeting UCSF but exceeding Milan criteria at pretransplant staging had a 5-year survival rate of only 48%, compared with 60% observed in the 272 patients within Milan criteria and with 37% in the 121 patients beyond both criteria.

The limitations of pretransplant imaging studies, exemplified by tumor understaging in 20% of patients, have been a major concern for liberalizing the existing criteria for OLT.[5] The UCSF group applied their proposed criteria according to preoperative imaging in 138 patients over a 5-year period; the 1- and 5-year recurrence-free probabilities were 95 and 91%, and the respective probabilities for recurrence-free survival were 91 and 80%.[14] The 106 patients with HCC meeting the Milan criteria (T1/2) had 1- and 5-year recurrence-free probabilities of 96 and 90%, respectively, compared with 93% at both 1 and 5 years for patients with HCC exceeding Milan but meeting UCSF criteria (T3A). Understaging by preoperative imaging was observed in 21% of T1/2 and 28% of T3A tumors. When explant tumor stage exceeded the UCSF criteria, the 1- and 5-year recurrence-free probabilities were 79 and 61%, compared with 98 and 97% within the UCSF criteria. Patients meeting T3A criteria did not have a significantly higher incidence of poorly differentiated tumor grade or vascular invasion.

In the current era of increasing demand and unrelenting organ shortage, the foundation of the debate regarding expansion of the Milan criteria for HCC may ultimately rest on what the transplant community would consider an acceptable survival after OLT for HCC. Some groups have proposed a 50% 5-year patient survival to be the minimum acceptable cutoff.[5] This mark may have been surpassed by the UCSF group, who have applied expanded criteria to benefit an additional 10% of patients with HCC with respect to posttransplant survival and tumor recurrence.

LIVING DONOR LIVER TRANSPLANTATION FOR HCC: EASTERN EXPERIENCE

Liver transplantation offers the best chance of cure for early unresectable HCC. However, its role has been limited by the shortage of deceased donor liver grafts, which is particularly severe in Asia, where the deceased donor organ rates are fewer than 5 donors per million population, compared with 10–35 donors per million population in Western countries.[15] In most Asian countries, HCC is the most common cancer and the most frequent indication for OLT, aggravating the unmet demand for liver grafts. The development of living donor liver transplantation (LDLT), especially adult-to-adult right lobe liver transplantation, has allowed more patients with HCC to benefit from OLT.[16] LDLT can theoretically provide an unlimited source of liver grafts and eliminate the uncertainty of prolonged waiting times and the risk of dropout due to tumor progression. However, LDLT is a novel treatment for HCC with unresolved issues regarding indications and results.

Recent studies on LDLT for HCC suggest favorable long-term survival results.[17,18] However, it remains unclear whether the outcome after LDLT for HCC is equivalent to that of deceased donor liver transplantation (DDLT). A study from a Korean group reported similar 3-year survival rates after LDLT and DDLT (91.4 vs 89.9%) in patients with tumors fulfilling the Milan criteria, after excluding perioperative mortality.[13] However, others have found significantly higher rates of tumor recurrence after LDLT compared with DDLT for HCC.[19] This may be related to selection bias, as LDLT eliminates the waiting period for grafts. In DDLT the waiting period provides time for a natural selection process in which patients with biologically more aggressive tumors drop out due to tumor progression. In addition, the ischemic-reperfusion injury associated with small-for-size grafts in LDLT and angiogenesis associated with liver regeneration may theoretically promote growth of tumors in the transplanted liver after LDLT, although the actual clinical impact of such biological processes remains unclear.[20,21]

Liver transplantation is conventionally offered to Child-Pugh class C patients with unresectable early HCC. Recently, there have been heated debates on whether liver transplantation should be used as first-line therapy for Child-Pugh class A patients with early HCC.[22] While some previous studies showed that liver transplantation for early HCC may achieve better survival compared with resection, this may be partly related to selection bias in favor of transplantation because patients with more aggressive tumors drop off the waiting list for DDLT.[19] Recent studies suggest that for patients with preserved liver function and early stage HCC, hepatic resection can achieve a 5-year survival rate of 70%, comparable to that after OLT.[13,23]

The availability of grafts from dedicated live donors has been considered one of the main arguments favoring LDLT as primary therapy for patients with early HCC and preserved liver function. However, even in Asian countries where LDLT is commonly performed, up to half of the patients with early HCC may not have suitable living donors for various reasons, including ABO-incompatibility, hepatitis serology, and patient refusal to accept living donation.[18] Furthermore, the risks of donor hepatectomy, with morbidity and mortality rates of 14–21% and 0.25–1%, respectively, should be carefully balanced against the benefit of LDLT.[19] Risking the life of a donor for HCC patients who have an alternative option of hepatic resection, which achieves long-term survival equivalent to LDLT, is ethically not acceptable to many Asian surgeons. Most Asian centers still consider resection as first-line treatment for HCC patients with preserved liver function and reserve LDLT as an option for salvage transplantation in patients with recurrent tumors.[13,23,24]

Another matter of debate in LDLT involves expanding the indications beyond the CMC or UCSF criteria. LDLT is currently being performed in some Asian centers for patients with HCC beyond the Milan criteria, with results that are expectedly worse than those for patients within the Milan criteria.[13,17] Some transplant surgeons argue that despite the poorer results, LDLT for advanced HCC may be justified, since donors voluntarily accept the risks of donor hepatectomy to dedicate a graft for HCC patients, who may otherwise have no effective treatment options. However, others argue that the medical profession should not relegate the issue to individual donor autonomy.[25] With the lack of clear data showing benefits of LDLT for advanced HCC, the medical community should take a conservative moral stand and limit the use of LDLT for HCC that meets the same criteria as DDLT.

LIVING DONOR LIVER TRANSPLANTATION FOR HCC: WESTERN EXPERIENCE

Over the past 10 years, LDLT has developed as an alternative to DDLT because of the scarcity of deceased donor livers. Patient survival after LDLT is similar to that after DDLT, despite data from the UNOS database showing lower post-LDLT graft survival, possibly due to the learning curve for LDLT and lower graft-to-recipient body weight ratio.[26] In the United States, enthusiasm for LDLT peaked in 2001, when more than 500 LDLTs were performed; the aftermath of a widely-publicized donor death in 2002 led to a nationwide retrenchment, with no more than 325 procedures per year since then. Nevertheless, LDLT has an important role in the treatment of HCC. While previously there was concern over possible tumor stimulation due to regeneration after LDLT, it appears that the type of graft (living vs deceased donor) has little, if any, impact on post-OLT tumor progression.

Typically, LDLT results in a liver graft that is smaller than the expected liver volume of the recipient. The outcome of a relatively small donor organ depends not only on graft size but also on the recipient's preoperative degree of liver failure and portal hypertension. Compared with patients awaiting transplant for end-stage cirrhosis, candidates with

HCC generally have better-preserved liver function and less portal hypertension, and are thus better able to tolerate a small graft.

Ready availability is the most important advantage of LDLT for HCC. Posttransplant tumor recurrence is tied to pretransplant tumor stage; progression of tumor while awaiting transplant can only worsen the prognosis. This fact is reflected in the United States allocation scheme for deceased donor livers, which accords priority to patients with HCC meeting the Milan criteria. Since adoption of the Model of End-Stage Liver Disease organ allocation policy in 2002, candidates with T2 HCC (1 nodule between 2 and 5 cm; or 2–3 nodules, all ≤3 cm) have enjoyed priority such that in many regions of the United States, waiting times are short, obviating the need for LDLT.[27] In some regions, however, longer waiting times and attendant higher dropout rates support the use of LDLT in cases of HCC within the Milan criteria.

The Milan criteria were adopted because they identify a subgroup of candidates with HCC for whom transplant results are similar to those in patients transplanted for end-stage cirrhosis without HCC. It is widely recognized, however, that many patients with HCC beyond the Milan criteria can be cured by OLT.[8,9] In the United States, adoption of expanded priority criteria for DDLT, as proposed by the UCSF group, is currently under consideration. LDLT can be undertaken in candidates who do not meet criteria for waiting list priority. Broadening criteria based on tumor size and number will inevitably lead to more recurrence; nevertheless, Roayaie et al. demonstrated 55% freedom from recurrence at 5 years in patients transplanted with HCC between 5 and 7 cm and no macroscopic vascular invasion.[28] Based on data such as these, many centers offer LDLT to patients with HCC meeting expanded criteria that are estimated to yield a 5-year survival of approximately 50%.[5]

SELECTION IN HCC: BIOLOGY OR MORPHOLOGY

The distinction between biology and morphology in simple terms can be described as behavior versus appearance. Ultimately, the behavior of HCC is the final deciding factor on patient outcome. The ability to predict the biology of HCC is desperately needed for patient selection in OLT. The current staging criteria for HCC takes into account tumor morphology but not tumor biology, with transplantable stages stratified according to tumor size and number. For treatment options other than liver transplantation (i.e., liver resection, chemotherapy, and cytoablative therapies), tumor morphology as described by the pathological TNM staging system is reasonably adequate. For liver transplantation, however, gross and microscopic morphology are inadequate for predicting outcomes because of the scarcity of the donor organs that must be judiciously allocated. The issue would be less significant if resources were unlimited.

Ideally, the TNM or morphology-based staging system would be able to stratify patients into homogeneous groups with the same outcomes. However, the current staging systems are not precise enough to segregate patients with HCC and cirrhosis into such homogeneous groups. As almost all patients with gross invasion of the hepatic venous system, positive lymph nodes, or metastatic disease experience recurrence and are therefore not candidates for transplantation, the N and M components of the TNM classification can immediately be eliminated from the organ allocation scheme. This leaves only the T component upon which we can base our biological prediction, namely tumor size and number.

In our efforts to refine our current staging systems, morphological or chemical factors have been studied, including microscopic vascular invasion, encapsulation, plasma albumin mRNA, and serum alpha-fetoprotein.[5] To date, however, none of these have improved upon the current systems. Part of the problem has been radiologic techniques are not yet sufficient to perfectly define tumor number and size and will never be able to determine microscopic vascular invasion. Moreover, many new staging systems require pretreatment biopsy, which poses a small but real risk of tumor seeding.

To understand the biological behavior and identify genes associated with survival after OLT, Marsh and colleagues at the University of Pittsburgh performed microdissection on explanted tissue and studied DNA mutations near 9 tumor-associated gene loci to create an index of cumulative mutational damage, termed the fractional allelic imbalance (FAI).[29,30] They found that FAI and vascular invasion were the strongest independent predictors of tumor-free survival. Thus, incorporation of gene mutational data allows desegregation of HCC patients from imprecise, morphology-based staging systems and allows improved prognostication.

CONCLUSIONS

While patients with early resectable HCC and preserved hepatic function should undergo surgical

resection, in those with unresectable disease due to underlying liver dysfunction, orthotopic liver transplantation (OLT) offers the best chance for cure. In the past 10 years, results of OLT have steadily improved because of careful patient selection pioneered by the introduction of the Milan criteria in 1996. Supported by studies showing that many patients with tumor stage beyond the Milan criteria can be cured by OLT, a number of expanded criteria have been proposed. While expanding the criteria for OLT allows more patients to be eligible for transplantation, arguments against expanding the criteria include the increased risk of vascular invasion and tumor recurrence at higher stages of HCC. The principal limitation of OLT for HCC is the shortage of deceased donor living grafts, especially in Asia. The development of LDLT has allowed more patients to benefit from OLT with favorable preliminary survival results. Given the shortage of organs available for OLT and lack of predictive power of currently used staging systems, improved prognostic tools are needed to predict outcomes after OLT. Molecular markers of cancer progression may add significant discriminatory power to the current staging systems and may improve organ allocation schemes for patients with HCC.

ACKNOWLEDGMENTS

Doctor V. Mazzaferro and Doctor S. Bhoori are partially supported by the Italian Association for Cancer Research (AIRC).

OPEN ACCESS

REFERENCES

1. Botha JF, Langnas AN. Liver transplantation for hepatocellular carcinoma: an update. *J Natl Compr Canc Netw* 2006; 8:762–7.
2. Ringe B, Pichlmayr R, Wittekind C, Tusch G. Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. *World J Surg* 1991; 2:270–85.
3. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; 11:693–9.
4. Jonas S, Bechstein WO, Steinmuller T, Herrmann M, Radke C, Berg T, Settmacher U, Neuhaus P. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology* 2001; 5:1080–6.
5. Bruix J, Fuster J, Llovet JM. Liver transplantation for hepatocellular carcinoma: Foucault pendulum versus evidence-based decision. *Liver Transpl* 2003; 7:700–2.
6. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; 6:1394–403.
7. Majno P, Mazzaferro V. Living donor liver transplantation for hepatocellular carcinoma exceeding conventional criteria: questions, answers and demands for a common language. *Liver Transpl* 2006; 6:896–8.
8. Broelsch CE, Frilling A, Malago M. Should we expand the criteria for liver transplantation for hepatocellular carcinoma—yes, of course!. *J Hepatol* 2005; 4:569–73.
9. Hiatt JR, Carmody IC, Busuttil RW. Should we expand the criteria for hepatocellular carcinoma with living-donor liver transplantation?—no, never. *J Hepatol* 2005; 4:573–7.
10. Decaens T, Roudot-Thoraval F, Hadni-Bresson S, Meyer C, Gugenheim J, Durand F, Bernard PH, Boillot O, Sulpice L, Calmus Y, Hardwigsen J, Ducerf C, Pageaux GP, Dharancy S, Chazouilleres O, Cherqui D, Duvoux C. Impact of UCSF criteria according to pre- and post-OLT tumor features: analysis of 479 patients listed for HCC with a short waiting time. *Liver Transpl* 2006; 12:1761–9.
11. Fernandez JA, Robles R, Marin C, Sanchez-Bueno F, Ramirez P, Pons JA, Garre MC, Perez D, Parrilla A, Navalon JC, Parrilla P. Can we expand the indications for liver transplantation among hepatocellular carcinoma patients with increased tumor size?. *Transplant Proc* 2003; 5:1818–20.
12. Leung JY, Zhu AX, Gordon FD, Pratt DS, Mithoefer A, Garrigan K, Terella A, Hertl M, Cosimi AB, Chung RT. Liver transplantation outcomes for early-stage hepatocellular carcinoma: results of a multicenter study. *Liver Transpl* 2004; 11:1343–54.
13. Hwang S, Lee SG, Joh JW, Suh KS, Kim DG. Liver transplantation for adult patients with hepatocellular carcinoma in Korea: comparison between cadaveric donor and living donor liver transplantations. *Liver Transpl* 2005; 10:1265–72.
14. Yao FY XL, Bass NM, Kerlan RK, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: a 5-year prospective study validating extended criteria applied to preoperative imaging. Hepatology 2006;(Suppl 1):191A.
15. de Villa VH, Lo CM, Chen CL. Ethics and rationale of living-donor liver transplantation in Asia. *Transplantation* 2003; 3(Suppl):S2–5.
16. Fan ST, Lo CM, Liu CL. Technical refinement in adult-to-adult living donor liver transplantation using right lobe graft. *Ann Surg* 2000; 1:126–31.
17. Todo S, Furukawa H. Living donor liver transplantation for adult patients with hepatocellular carcinoma: experience in Japan. *Ann Surg* 2004; 3:451–9.
18. Lo CM, Fan ST, Liu CL, Chan SC, Wong J. The role and limitation of living donor liver transplantation for hepatocellular carcinoma. *Liver Transpl* 2004; 3:440–7.
19. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Difference in tumor invasiveness in cirrhotic patients with hepatocellular carcinoma fulfilling the Milan criteria treated by resection and transplantation: impact on long-term survival. *Ann Surg* 2007; 1:51–8.
20. Man K, Fan ST, Lo CM, Liu CL, Fung PC, Liang TB, Lee TK, Tsui SH, Ng IO, Zhang ZW, Wong J. Graft injury in relation to graft size in right lobe live donor liver transplan-

tation: a study of hepatic sinusoidal injury in correlation with portal hemodynamics and intragraft gene expression. *Ann Surg* 2003; 2:256–64.
21. Yang ZF, Poon RT, Luo Y, Cheung CK, Ho DW, Lo CM, Fan ST. Up-regulation of vascular endothelial growth factor (VEGF) in small-for-size liver grafts enhances macrophage activities through VEGF receptor 2-dependent pathway. *J Immunol* 2004; 4:2507–15.
22. Poon RT. Optimal initial treatment for early hepatocellular carcinoma in patients with preserved liver function: transplantation or resection?. *Ann Surg Oncol* 2007; 2:541–7.
23. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg* 2002; 3:373–82.
24. Takada Y, Ueda M, Ito T, Sakamoto S, Haga H, Maetani Y, Ogawa K, Kasahara M, Oike F, Egawa H, Tanaka K. Living donor liver transplantation as a second-line therapeutic strategy for patients with hepatocellular carcinoma. *Liver Transpl* 2006; 6:912–9.
25. Volk ML, Marrero JA, Lok AS, Ubel PA. Who decides? Living donor liver transplantation for advanced hepatocellular carcinoma. *Transplantation* 2006; 9:1136–9.
26. Thuluvath PJ, Yoo HY. Graft and patient survival after adult live donor liver transplantation compared to a matched cohort who received a deceased donor transplantation. *Liver Transpl* 2004; 10:1263–8.
27. Wiesner RH, Freeman RB, Mulligan DC. Liver transplantation for hepatocellular cancer: the impact of the MELD allocation policy. *Gastroenterology* 2004; 5(Suppl 1):S261–7.
28. Roayaie S, Frischer JS, Emre SH, Fishbein TM, Sheiner PA, Sung M, Miller CM, Schwartz ME. Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 centimeters. *Ann Surg* 2002; 4:533–9.
29. Marsh JW, Finkelstein SD, Demetris AJ, Swalsky PA, Sasatomi E, Bandos A, Subotin M, Dvorchik I. Genotyping of hepatocellular carcinoma in liver transplant recipients adds predictive power for determining recurrence-free survival. *Liver Transpl* 2003; 7:664–71.
30. Finkelstein SD, Marsh W, Demetris AJ, Swalsky PA, Sasatomi E, Bonham A, Subotin M, Dvorchik I. Microdissection-based allelotyping discriminates de novo tumor from intrahepatic spread in hepatocellular carcinoma. *Hepatology* 2003; 4:871–9.